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Cover Page

Statistical Analysis Plan

REGAL

A Real World Evaluation of the ELUVIA Drug Eluting Stent in All-Comers With Superficial Femoral Artery and Proximal Popliteal Artery Disease

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Boston Scientific

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A Real World Evaluation of the ELUVIA Drug ElutinG Stent in All-Comers with Superficial FemoraL Artery and Proximal Popliteal Artery Disease (REGAL)

QUANTICS REFERENCE 1273

STATISTICAL ANALYSIS PLAN

VERSION 1.0

04 May 2022

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STATISTICAL ANALYSIS PLAN FOR REGAL

QUANTICS REFERENCE NUMBER 1273

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Boston Scientific

CONTENTS

SECTION 1: INTRODUCTION & TERMS

1.1 ABBREVIATIONS

ABI	Ankle Brachial Index
AE	Adverse Event
BSC	Boston Scientific Corporation
CEC	Clinical Events Committee
CIN	Contrast-Induced Nephropathy
CIP	Clinical Investigational Plan
CSR	Clinical Study Report
DES	Drug Eluting Stent
DUS	Duplex Ultrasound
GCP	Good Clinical Practice
ITT	Intent-to-treat
MAE	Major Adverse Event
PAD	Peripheral Arterial Disease
PP	Per protocol
PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio
RCC	Rutherford-Becker clinical classification
RVD	Reference Vessel Diameters
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Stent Delivery System
SFA	Superficial Femoral Artery
TBI	Tibial Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

WIQ	Walking Impairment Questionnaire

1.2 INTRODUCTION

This document describes the statistical analysis and reporting plan for data from REGAL: A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with SuperficiaL Femoral Artery and Proximal Popliteal Artery Disease [1]. The study is a prospective, multi-center Post-Market Clinical Follow-up (PMCF) trial providing additional data including health economics data to support the use of the ELUVIA stent in the treatment of lesions located in the femoropopliteal arteries.

As described in the ICH E9 guideline [2], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the study protocol [1], and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Details of the procedures that will be followed by Quantics when undertaking data receipt, analysis and reporting are described in Quantics SOPs [3] [4].

Any amendments to the SAP will be made prior to database lock.

Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report.

Quantics Consulting Limited will perform the statistical analyses and are responsible for the production and quality control of all tables, listings, and figures.

1.2.1 BACKGROUND

Peripheral Arterial Disease (PAD) is the third leading cause of cardiovascular morbidity after myocardial infarction and stroke. Over the past decade, percutaneous catheter-based techniques have improved such that acute procedural success is high even in complex anatomy. This has led to the adoption of endovascular treatment as the first strategy treatment in PAD-patients.

The femoropopliteal segment is a challenging vascular territory and has been among the least effective of all endovascular procedures in terms of long-term patency. In recent years, however, improvements in device technology and the skill-sets of the interventionalists have facilitated the treatment of complex lesions, including long-segment chronic occlusions with or without moderate calcification. More specific, the application of self-expanding nitinol stent technology seemed to improve the safety and durability of stenting in the SFA due to its unique properties such as flexibility, persistent radial force when oversized to a vessel, and ability for crush recovery in these high flexion and torsion force areas in the femoropopliteal arteries. In addition, self-expanding nitinol stents are not as prone to external compression as are balloon-expandable stents.

Although above the knee use of nitinol Bare Metal Stents is safe and feasible, it is evidently associated with significant neointimal hyperplasia and early restenosis, which may be due to the chronic external forces on the vessel/stent interface resulting in a chronic stimulus for restenosis9. Therefore, the interest of investigators turned towards pharmaceuticals such as paclitaxel to suppress neointimal growth and restenosis after stent deployment. DES technology was developed to prevent early thrombosis and late luminal loss to potentially improve long-term patency rates for SFA.

1.2.2 ELUVIA STENT SYSTEM

Boston Scientific Corporation developed the ELUVIA stent, a paclitaxel-eluting, self-expanding nitinol stent, for use in the femoropopliteal arteries.

The ELUVIA Stent System leverages many successful BSC programs with global commercial approval for safe and efficacious use in subjects, and received CE-mark in February 2016. The ELUVIA stent and Stent Delivery System (SDS) is leveraged from the Innova™ Stent System, the drug coating polymers are leveraged from the PROMUS Element/PROMUS Element Plus Stent System, while the active pharmaceutical compound (paclitaxel) is leveraged from the TAXUS Element/ION Stent System.

SECTION 2: STUDY OBJECTIVES

The objective of the REGAL study is to collect additional data including health economics data to support the use of the ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions.

SECTION 3: CIP SUMMARY

3.1 STUDY DESIGN

The REGAL study is a European, prospective, multi-center Post Market Clinical Follow-up trial providing additional data including health economics data to support the use of the ELUVIA stent in the treatment of lesions located in the femoropopliteal arteries.

The ELUVIA stent is CE-marked and commercially available in the regions included in this study, and has already demonstrated its safety and effectiveness for treatment of symptomatic de-novo or restenotic lesions in the native SFA and/or PPA with reference vessel diameters (RVD) ranging from 4.0-6.0 mm.

3.2 SCALE AND DURATION

500 subjects will be enrolled in the REGAL study to receive treatment with the ELUVIA Stent system.

The study will be conducted in up to 30 study centers in up to 10 European countries.

All subjects will be screened according to the protocol inclusion and exclusion criteria and will be considered eligible to be enrolled in the study once a signed informed consent form is in place.

If the subject is found to not meet the inclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be included in the study, nor should the subject be followed post-procedure per protocol.

A subject is considered enrolled when the ELUVIA stent system is advanced into the patient's vasculature.

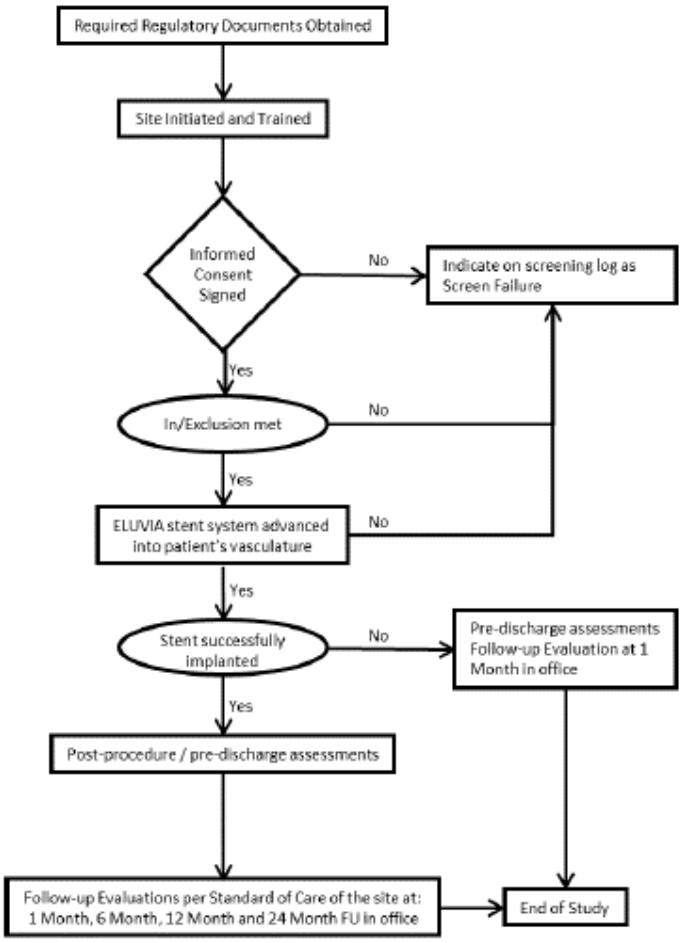
Clinical follow-up is required as per standard of care and data will be collected at the following time points: pre-discharge, 1 month, 6 months, 12 months and 24 months post index procedure.

Subjects who are enrolled but an ELUVIA stent was not successfully implanted will be followed through the 1-month follow-up visit only. Data for assessment of major adverse events (MAE) will be collected for these subjects; other testing is not required.

The enrollment period is expected to last approximately 12 months. No investigative site will be allowed to enroll more than 20 percent (100 subjects) of the total study population. The study will be considered complete after all subjects have completed the 24-month (2-year) follow-up visit, were discontinued prior to the 24-month (2-year) follow-up visit, have died, or the last 24-month (2-year) follow-up visit window is closed.

It is estimated that it will take approximately 4 years to complete this study.

3.3 STUDY FLOW CHART



Data to be collected are shown in the schedule below.

Data collection schedule per standard of care							
	Pre-procedure[2]	During Index Procedure Day 0	Pre-Discharge	1MFU (Day 15-90)	6MFU (Day 91-273)	12MFU (Day 274-456)	24MFU (Day 457-760
Informed Consent[1]	X						
In/exclusion criteria	X	X					
Demographics & Medical History, Height and Weight	X						
Serum Creatinine	X						
Platelet count	X						
Pregnancy test[2]	X						
ABI	X			X[3]	X	X	X
RCC (Rutherford-Becker clinical classification)	X			X	X	X	X
WIQ	X			X	X	X	X
EQ-5D-5L	X			X	X	X	X
DUS[4]					X	X	X
Health Economics		X		X	X	X	X
Medication	X	X	X	X	X	X	X
Adverse Events[5]	X	X	X	X	X	X	X

1.Subject's consent obtained and informed consent form signed prior to any study-specific tests or procedures
2.Performed within 30 days of procedure, except urine or blood pregnancy test required for females of childbearing potential performed within 7 days of procedure
3.ABI measurement may be collected immediately post-procedure through 1 Month Follow-up window (Day 0 – 90)
4.DUS images will be sent to the respective core lab for analysis. Follow-up ultrasounds will not be required for any subject who underwent bypass surgery of the target lesion during the 24-month follow-up timeframe, or has a documented occluded stent.
5.Reporting required through the end of study for UADEs and (S)ADEs/Device Deficiencies.

3.4 STUDY POPULATION

3.4.1 SUBJECT SELECTION

The Intended population for the REGAL study are 'real world' patients with symptomatic de novo, restenotic, or (re)occluded lesions in the native SFA and/or PPA with RVD ranging from 4.0-6.0 mm, suitable for endovascular treatment.

3.4.2 INCLUSION CRITERIA

For inclusion in the study subjects must fulfil ALL of the following criteria:

1. Subjects age 18 and older
2. Subject is willing and able to provide written consent before any study-specific test or procedure is performed and agrees to attend all follow-up visits
3. De novo, restenotic or (re)occluded lesions in the native femoro-popliteal arteries, with RVD ranging from 4.0-6.0 mm, suitable for endovascular treatment

3.4.3 EXCLUSION CRITERIA

Subjects are excluded if ANY of the following criteria are met:

1. Subject is pregnant or planning to become pregnant during the course of the study
2. Life expectancy of less than 1 year (which is defined as documented life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical follow-up, limit the subject's compliance with the standard of care follow-up, or impact the scientific integrity of the trial)
3. Known allergy to the ELUVIA stent system or any of its components, concomitant medication, contrast agents (that cannot be medically managed)
4. Subject enrolled in an investigational study that has not reached primary endpoint at the time of enrollment or that clinically interferes with the current study assessments (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies)

3.5 STUDY ASSESSMENTS

Health-Economics data will be collected as follows

- Walking Improvement and Quality of Life improvement at 1 month, 6 months, 12 months and 24 months assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D-5L™ from baseline
- Changes in healthcare utilization over time:
    - Number of physician visits for PAD of the target vessel
    - Number of amputations of target limb
    - Number of TVRs
    - Number of days in rehabilitation, related to PAD
    - Number of days in hospital, related to PAD
- Rate of Primary and Secondary Sustained Clinical Improvement at 1 month, 6 months, 12 months and 24 months assessed by changes in Rutherford Classification from baseline, combined with the need for repeat TLR
- Rate of Hemodynamic Improvement at 1 month, 6 months, 12 months and 24 months assessed by changes in Ankle-Brachial Index (ABI) from baseline
    - Defined as improvement of ABI by ≥ 0.1 or to an ABI ≥ 0.90 as compared to the pre-procedure value without the need for repeat revascularization.

Additional assessments will be collected as follows:

- Technical success defined as delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually

- Procedural success defined as technical success with no MAEs noted within 24 hours of the index procedure
- MAE rate (and individual components) at each time point, defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR)
- Primary Patency and Assisted Primary Patency at 6 months, 12 months and 24 months
    - Vessel patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.
    - A PSVR >2.4 suggests >50% stenosis.
    - The stented segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the stented segment.
    - All DUS will be assessed by an independent core laboratory.
    - In case of multiple lesions treated, the lesion with the highest final % stenosis at the end of the index procedure will be used for the main (by subject) patency analyses. Primary patency will also be presented over all lesions treated.
- Clinically-driven TLR and clinically-driven Target Vessel Revascularization (TVR) Rate at each follow-up visit
    - Clinically-driven: A re-intervention within 5 mm proximal or distal to the original treatment segment for > 50% angiographic diameter stenosis in the presence of recurrent symptoms (≥ 1 change in Rutherford class) or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. Tibial Brachial Index (TBI) allowed in cases of incompressible vessels
- Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point
- Distribution of Rutherford Class during follow-up as compared to baseline at 1 month, 6 months, 12 months and 24 months

SECTION 4: STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The intent-to-treat population (ITT) consists of all subjects enrolled in the study in whom the ELUVIA stent was implanted. This will be used in the primary analysis of all assessments. The per-protocol (PP) population consists of all the ITT subjects without any major protocol deviations. If the PP is not identical to the ITT population, then all assessments will be analyzed for the PP population as well.

4.2 TIME POINT ANALYSIS

No formal interim analyses for early stopping based on effectiveness or futility will be performed. Statistical analysis may be performed at specific time points throughout the duration of the trial. The statistical analysis plan will be updated to reflect any planned analysis prior to performing the analysis.

4.3 GENERAL STATISTICAL METHODS

All statistical analyses will be performed using SAS 9.4 (Copyright © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

The number evaluated, mean, standard deviation, minimum and maximum values will be presented for continuous and / or ordinal variables. Counts, and percentages will be presented for categorical variables.

The results for all assessments will be given as descriptive statistics and will not be tested using formal hypotheses, with the exception of the WIQ assessments, subgroup analyses and multivariable analyses as described below.

4.3.1 ADEQUATE FOLLOW UP FOR CALCULATION OF AE RATES

For the calculation of the AE rate at each time point, the numerator will include patients with AEs, that occurred at any time from the date of the procedure up until the cut-off point defined in the second column in the table below. The denominator will include subjects with AEs or with adequate follow up, as defined in the table below, where follow up is the difference between the date of the last follow up visit and the date of the procedure.

Time point	Days for Adequate Follow-Up	Follow-Up Cut-Off for AEs
1 month	15	90 Days
6 months	91	273 Days
12 months	274	456 Days
24 months	457	760 Days

4.3.2 BASELINE VALUE AND CHANGE FROM BASELINE

The baseline value for an assessment is the value recorded at the Pre-procedure visit. For continuous variables, Changes from baseline at 1, 6, 12 and 24 months are calculated for each subject as the value at the time point minus the value at baseline.

4.3.3 DEGREE OF DIFFICULTY SCORES

The WIQ questionnaire characterizes subjects' self-reported degree of difficulty in walking and contains 4 sections of questions: Walking Impairment (e.g. 1 PAD/Peripheral Arterial Disease specific item and a list of differential diagnoses), Walking Distance (7 items), Walking Speed (4 items), and Stair Climbing (3 items).

These responses are ranked on a scale of 0 to 4, (0=unable to do, 4=no difficulty). Subjects are instructed to give the response "unable" when the limitation was due to claudication pain. A weighted-average score will be constructed for each section, using the weights specified in table 8.3.4 below.

For an example of summarizing Walking Distance, if a subject responds with a 3 (slight difficulty) for the first 5 items, a 2 (some difficulty) for walking 900 feet, and a 0 (unable to do) for walking 1,500 feet, the summary score for this subject will be calculated as:

The raw score: 3*20 + 3*50 + 3*150 + 3*300 + 3*600 + 2*900 + 0*1,500 = 5,160

The Maximal score for Walking Distance: 4*(20 +50 +150 +300 +600 +900 +1,500) = 14,080

The summary score: 5,160/14,080 = 36.65%

The summary scores for Walking Speed (maximal score of 46) and Stair Climbing (maximal score of 24) are similarly derived. The overall Walking Impairment score will be calculated as the average of the Walking Distance, Walking Speed, and Stair Climbing scores. Several symptoms that could limit walking performance are also characterized (in question 1), and the degree of difficulty in walking caused by a symptom is graded. The specific symptoms evaluated include pain or aching in the calf or thigh (characteristic of intermittent claudication); pain, stiffness or aching of joints (arthritis); weakness in the legs (neuromuscular dysfunction); and chest pain, dyspnea, or palpitations (typical of cardiopulmonary disorders). These questions enable assessment of comorbid disorders that could limit ambulation in addition to claudication. No aggregate summary score is developed for the questions relating to symptoms because they are not a ranked series, but the data for the claudication symptom (PAD specific question) will be presented as a percentage (where a score of zero is 0%, 1 is 25%, 2 is 50%, 3 is 75% and 4 is 100%).

4.3.4 DEGREE OF DIFFICULTY WEIGHTS

Question	Weight
Walking Distance subscale	
Walking indoors such as around your home?	20
Walking 20 meters/ 50 feet?	50
Walking 50 meters/ 150 feet (1/2 block)?	150
Walking 100 meters/ 300 feet (1 block)?	300
Walking 200 meters/ 600 feet (2 blocks)?	600
Walking 300 meters/ 900 feet (3 blocks)?	900
Walking 500 meters/ 1500 feet (5 blocks)?	1500
Maximum possible total score	14080
Walking Speed subscale	
Walking 100 meters/ 1 block slowly?	1.5
Walking 100 meters/ 1 block at an average speed?	2
Walking 100 meters/ 1 block quickly?	3
Running or jogging 100 meters/ 1 block?	5
Maximum possible total score	46
Stair Climbing subscale	
Climbing 1 flight of stairs?	1
Climbing 2 flights of stairs?	2
Climbing 3 flights of stairs?	3
Maximum possible total score	2

4.4 SAMPLE SIZE CALCULATION

No formal sample size calculation was performed. 500 subjects are to be enrolled and treated at up to 30 centers in up to 10 European countries.

4.5 MULTIVARIABLE ANALYSIS

For binary endpoints of interest (12-month primary patency and 12-month MAE-free), univariate and multivariable analyses will be performed to assess the effect of potential predictors in a logistic model. Univariate logistic regression analyses will be conducted for the covariates listed below. The results will be tabulated in ascending order of p-value. All covariates with $p < 0.1$ in the univariate analyses will be included in a multivariable logistic regression analysis. A backwards elimination approach will be used to determine the variables in the final multivariate model, where the variable with highest p-value will be excluded one by one until all variables in the model have $p < 0.1$. Odds ratios will be calculated for variables in the final model. No corrections will be made for multiplicity and no formal conclusions will be drawn from this analysis. Analysis will be conducted as complete-case, with patients missing any of the relevant variables for a given univariate or multivariable analysis excluded. In the case that the regression model fails to converge (due to very small counts or quasi-complete separation), levels may be combined or excluded. Levels/units for each variable are identified below, but may be altered dependent on the data.

Variable	Levels/units
Gender	Male, Female, Intersex/unknown
Medically treated for diabetes	Yes (treated with insulin or oral agent) No/Non diabetic
Renal insufficiency	Yes No/Unknown
History of hyperlipidemia requiring medication	Yes No/Unknown
History of hypertension requiring medication	Yes No/Unknown
Smoking history	Current/previous/unknown Never
Rutherford Score	2-3, 4-6
Peripheral vascular history	History of peripheral vascular surgery or endovascular intervention in target limb/vessel

Variable	Levels/units
	No history of surgery or intervention in target limb/vessel
CTO at baseline (stenosis = 100%)	Yes, No
Lesion length	≤150 mm vs. >150 mm
Predilation	Yes, No
TASC classification	A-B, C-D
Treatment approach	True lumen, subintimal

4.6 SUBGROUP ANALYSIS

Key study data (primary patency, MAE rate, baseline characteristics) will be presented according to subgroups of interest (e.g. those found to be significant in the univariate/multivariate analysis). Primary patency and MAE rate will be compared between the subgroups via a Chi-square test. Subjects with missing data on a particular covariate will be excluded from the subgroup analyses. Analyses of other assessments may also be performed by subgroups

4.7 STUDY ENDPOINTS

4.7.1 HEALTH ECONOMIC ASSESSMENTS

Questionnaires:

- For the WIQ, the observed value will be summarized at baseline and at 1, 6, 12 and 24 months, and the change from baseline will be summarized at 1, 6, 12 and 24 months for:
    - Degree of difficulty for distance
    - Degree of difficulty for speed
    - Degree of difficulty for climbing
    - Walking impairment

The change from baseline in WIQ Degree of Difficulty endpoints (distance, speed, stair climbing, walking impairment) will be compared with zero using a one-sample, two-sided t test. Percentage of patients observing an improvement in scores will also be presented.

- For the EQ-5D-5L™, the number and percentage in each category will be summarized at baseline and at 1, 6, 12 and 24 months, and the number showing improvement, defined as improving by at least one category from baseline, will be summarized at 1, 6, 12 and 24 months for:
    - Mobility
    - Self-care
    - Usual activities
    - Pain / discomfort
    - Anxiety / depression
- EQ5D Index Values (model from the US) on a scale from 1:100 (worst to best). For the EQ-5DTM index value, the EQ-5D-5L Index Value Calculator (developed by the EuroQol Group) will be utilized.
- The EQ Visual Analogue Scale will be summarized as a continuous variable at baseline and at 1, 6, 12 and 24 months, and the change from baseline will be summarized at 1, 6, 12 and 24 months.

Health economic data:

- For the following assessments, the observed value (since last visit) and the cumulative value (total since discharge) will be summarized at 1, 6, 12 and 24 months:
    - Number of physician visits for PAD of the target vessel
    - Number of amputations of target limb
    - Number of TVRs
    - Number of days in rehabilitation, related to PAD
    - Number of days in hospital, related to PAD

Primary and Secondary Sustained Clinical Improvement:

- The Rutherford-Becker Clinical Classification will be:
    - summarized as a categorical variable at baseline and at 1, 6, 12 and 24 months
    - presented as a shift table comparing baseline with 1, 6, 12 and 24 months

Hemodynamic Improvement:

- The ABI for the treated limbs will be:
    - summarized as a continuous variable at baseline and at 1, 6, 12 and 24 months
    - categorized as improvement of ABI by ≥ 0.1 or to an ABI ≥ 0.90 as compared to the pre-procedure value without the need for repeat revascularization, and summarized as a categorical variable at 1, 6, 12 and 24 months.

Clinical improvement / deterioration:

- The following will be summarized as categorical variables
    - Primary sustained clinical improvement:
        - an improvement in Rutherford classification of one or more categories as compared to baseline without the need for repeat TLR.
    - Secondary sustained clinical improvement:
        - an improvement in Rutherford classification of one or more categories as compared to baseline including those subjects with repeat TLR.
    - Clinical deterioration:
        - downgrade in Rutherford classification of one or more categories as compared to baseline.
    - No change in Rutherford classification from baseline

4.7.2 ADDITIONAL ASSESSMENTS

Success rates:

- Technical success
    - Defined as delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually.
- Procedural success
    - technical success+ no MAE within 24hrs

Adverse event rates:

- Of subjects with adequate follow up (see table above), the number and percentage who experienced at least one AE since the start of the procedure (artery access) will be summarized at 1, 6, 12 and 24 months for the following categories of AE:
    - MAE
        - all causes of death
        - target limb major amputation
        - TLR
    - Unanticipated AE
    - Serious AE
    - Device-related AE
    - Procedure-related AE
    - Stent thrombosis

Primary Patency:

- The number and percentage of subjects with the following will be summarized at 6, 12 and 24 months:

- Primary patency: DUS PSVR ≤ 2.4 or stenosis category is patent when PSVR is missing in the absence of clinically-driven TLR or bypass of the target lesion.
- Assisted Primary Patency: primary patency using the DUS assessment among subjects without clinically-driven TLRs due to bypass or complete occlusion.

- The number and percentage of subjects with the following will be summarized at 6, 12 and 24 months:
  - Clinically-driven TLR
  - Clinically-driven TVR

4.8 BASELINE DATA ANALYSIS

Baseline covariates will be summarized for this study. Subject baseline demographics and clinical characteristics, site-reported and core lab reported lesion characteristics, procedure assessment, device information, and medication usage will be summarized using descriptive statistics.

4.9 GENERAL STATISTICAL METHODS

Subjects with missing DUS data at 12 months were imputed as patent if a later DUS assessment demonstrated patency, provided they did not experience a clinically-driven TLR prior to that assessment. All subjects with available data will be used in the statistical analyses. Missing event dates are discussed below. In case of all other missing data, subjects will be excluded from the specific analysis for which no data is available. No other imputation will be performed for these missing data.

4.9.1 MISSING EVENT DATES CONSIDERATIONS

All event rates will be calculated relative to the date of procedure, and only treatment emergent (i.e. post-procedure) events will be reported.

When event dates are missing or partially missing, in the first instance, efforts will be made to obtain the dates by liaison with safety and/or data management representatives to query sites for missing data. Failing this, missing and partial missing dates may be handled as using the worst case scenario as follows:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.

Partial Date Description	Action Taken
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

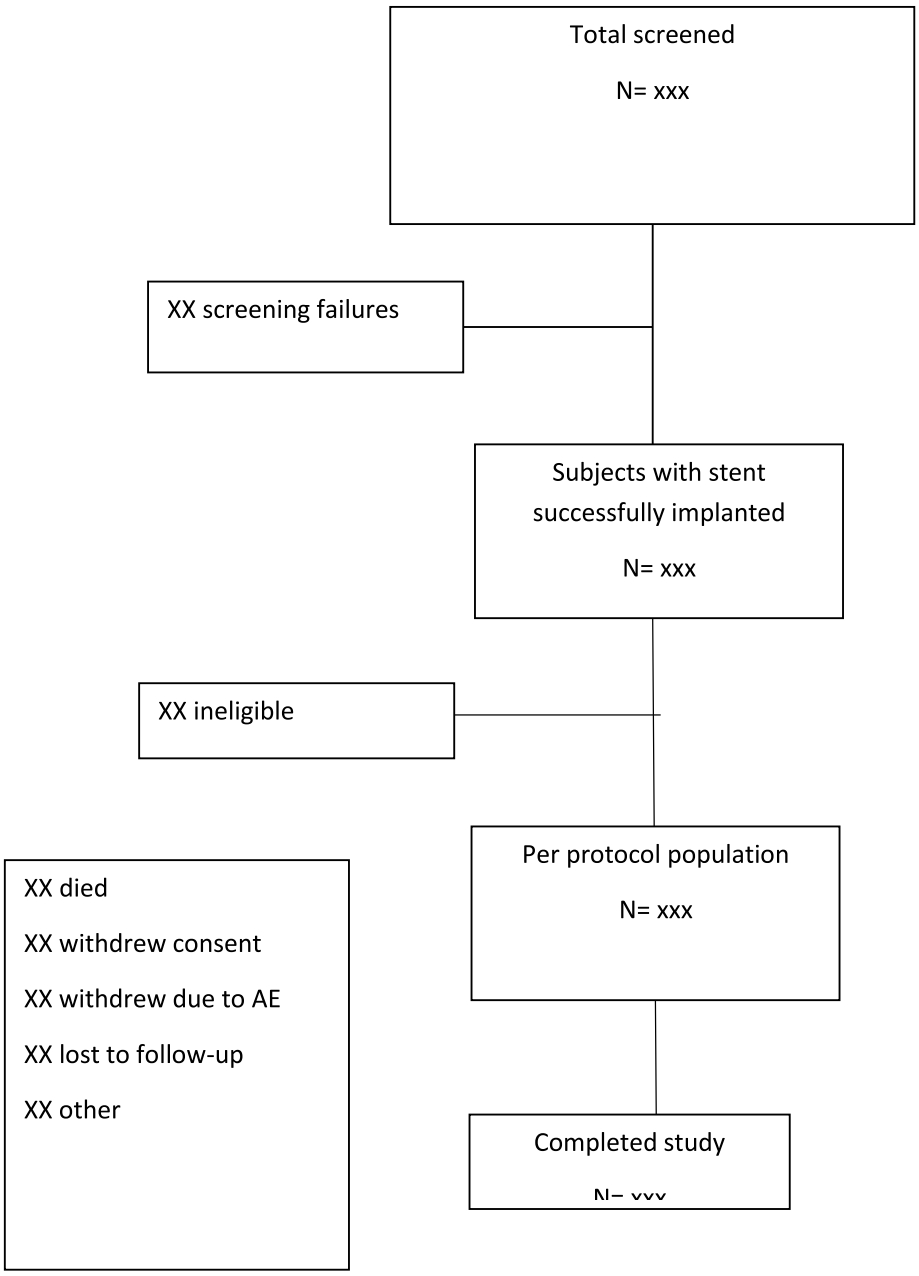
SECTION 5: LIST OF TABLES, LISTINGS AND FIGURES

The format and structure of all tables and listings is contained in a separate document. These detailed specifications can undergo minor revisions during the production phase without needing to revise the SAP. Minor revisions are defined as revisions that do not invalidate any of the specifications in section 4.

Table	Title
1	Disposition
2	Demographics and clinical characteristics
3	Medical history
4	Target lesion characteristics
5	Index procedure assessment
6	Technical and procedural success
7	WIQ observed and change from baseline (1, 6, 12, 24 months)
8	EQ-5D-5L observed and change from baseline (1, 6, 12, 24 months)
9	Healthcare utilization: at 1, 6, 12, 24 months
10	Healthcare utilization: cumulative at 1, 6, 12, 24 months
11	Rutherford-Becker Clinical Classification: actual at baseline, 1, 6, 12, 24 months
12	Rutherford-Becker Clinical Classification: shift table baseline to 1, 6, 12, 24 months
13	Clinical improvement / deterioration
14	Ankle Brachial Index, Hemodynamic Improvement: (1, 6, 12, 24 months) by limb
15	Primary patency and assisted primary patency at 6, 12, 24 months
16	Unanticipated, Serious, Device/procedure related AE at 1, 6, 12, 24 months
17	Protocol Deviation by Deviation Type and Country
18	CEC Adjudicated Adverse Events
19	Univariate and multivariate logistic regression analysis: MAE free at 12 months
20	Univariate and multivariate logistic regression analysis: Primary patency at 12 months
21	Summary of Primary patency and MAE at 12 months by subgroup
22+	Principal results and baseline summary by subgroups
Listing	Title
1	Non-serious adverse events
2	Serious adverse events
3	Protocol deviations
4	Subjects with total occlusion at baseline
5	Healthcare Utilization
6	List of all suspicions of serious adverse device effects (including USADE) and list of serious adverse events
Figure	Title
1	Subject disposition

Section 6: FIGURE SHELLS

Figure 1. Subject disposition



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[2] CPMP/ICH/363/96, “Statistical Principles for Clinical Trials, ICH Guideline Topic E9; Note for Guidance on Statistical Principles for Clinical Trials,” September 1998.

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